CLINICAL PHARMACOLOGY AND PHARMACOMETRICS REVIEW

NDA, BLA:	NDA 22187/S-009
Submission Date:	9/29/2011
Brand Name	Intelence®
Generic Name:	Etravirine (formerly TMC125)
Formulation (Strengths):	Tablets (25 mg, 100 mg, and 200 mg)
Applicant:	Janssen Pharmaceuticals Inc.
Indication:	Treatment of HIV-1 infection in antiretroviral-experienced pediatric patients
Intended Population:	Children and Adolescents 6 to <18 years of age
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I. Executive Summary

This review evaluates Studies TMC125-C126 and TMC125-C213 to determine if the applicant's proposed pediatric doses are appropriate.

A. Recommendation

The Office of Clinical Pharmacology has reviewed the information submitted to NDA 22187/S-009. The supplement is approvable from a clinical pharmacology perspective.

INTELENCE (etravirine), a non-nucleoside reverse transcriptase inhibitor (NNRTI), is currently approved for the treatment of HIV-1 infection in antiretroviral treatment-experienced adult patients, in combination with other antiretroviral (ARV) agents. The approved dose of etravirine in adults is 200 mg BID (2 x 100 mg tablets or 1x 200 mg tablet), taken orally with a meal.

The applicant is proposing to extend the indication to children and adolescents of 6 to less than 18 years based on the results of the following two studies:

- TMC125-C126, a Phase 1 dose-finding study of etravirine in children and adolescents of 6 to less than 18 years
- TMC125-C213, a Phase II study investigating the safety, efficacy and pharmacokinetics of etravirine in children and adolescents of 6 to less than 18 years.

The data included in the aforementioned studies support the extension of the indication to the use of etravirine as a component of ARV therapy in HIV-1 infected treatment-experienced children and adolescents aged 6 to less than 18 years. The applicant has proposed pediatric doses (Table 1) in these age groups that attain comparable exposure to that observed in adults at the approved dose. The doses of etravirine proposed for HIV-1 infected treatment-experienced children and adolescents are appropriate.

Table 1: Proposed etravirine dose for pediatric patients 6 to less than 18 years of age

Weight	Dose
16 to < 20 kg	100 mg b.i.d.
20 to < 25 kg	125 mg b.i.d.
25 to < 30 kg	150 mg b.i.d.
≥ 30 kg	200 mg b.i.d.

The applicant submitted data supporting a new 25 mg tablet formulation to allow for proposed pediatric dosing, which is acceptable from clinical pharmacology perspective. Currently, etravirine is approved as a tablet formulation in two different strengths: 100 mg and 200 mg. The active and the inactive ingredients of the 25 mg tablet are proportional to the approved 100 mg and 200 mg tablets, and the relative bioavailability study for the 25 mg tablet was previously reviewed (See Clinical Pharmacology Review for the original NDA). In addition, the 25 mg formulation was also used in the pediatric trials.

B. Phase IV Commitments

None.

C. Question-Based Review Summary

This question-based review summarized the reviewer's clinical pharmacology and pharmacometrics evaluation of the appropriateness of the proposed pediatric doses.

Etravirine, an NNRTI, is currently indicated for the treatment of HIV-1 infection in ARV treatment-experienced adult patients including those with NNRTI resistance, in combination with other ARV agents. The approved dosing regimen for adults is 200 mg taken twice daily orally following a meal. The submitted data in this application support extension of the indication to the use of etravirine as a component of ARV therapy in HIV-1 infected treatment-experienced children and adolescents aged 6 to less than 18 years.

To evaluate the appropriateness of the proposed pediatric dosage the following key questions were addressed:

1. Do the proposed pediatric etravirine doses attain comparable exposure to that achieved in adults at the approved adult dose?
2. Does the exposure-response (antiviral activity) relationship for etravirine support the proposed doses in children and adolescents?
3. Is the increased incidence of rash in pediatric subjects as compared with adult subjects explained by demographics, etravirine exposure, or other covariates?

In addition, analytical site and clinical site inspections were conducted to ensure the validity of the etravirine exposure data used in this evaluation. For this submission, approval is based on bridging etravirine exposures in pediatrics to that observed in adults. Therefore, the validity of the etravirine pharmacokinetic evaluation is pivotal for approval of etravirine use in pediatric patients. The inspection results are addressed in the following question:

4. Did the etravirine inspections indicate that the quality of the pharmacokinetic evluations were acceptable?

Question 1: Do the proposed pediatric etravirine doses attain comparable exposure to that achieved in adults at the approved adult dose?

Yes. Etravirine pediatric dose was determined by matching etravirine exposure in pediatric subjects to the adult exposure at the approved 200 mg BID dose, supported by efficacy and safety data from Study TMC125-C213. The population PK analyses demonstrated that in pediatric subjects ages 6 to less than 18 years, the proposed etravirine doses (b) (4) Table 1) in combination with other ARV drugs provided comparable etravirine exposure to that observed in HIV-1 infected treatment-experienced adults at the approved dosing regimen (200 mg twice daily) used in the DUET trials (Table 2).

Table 2: Comparison of etravirine pediatric exposure (Study TMC125-C213) and adult exposure

	Pediatrics (6 - <12 years)	Pediatrics (12 - <18 years)	Adults (DUET-1 and DUET-2)
N	41	60	575
AUC_{12h} (ng.h/mL)			
Mean (SD)	5764 (4404)	4956 (4480)	5506 (4710)
Median (Min; Max)	5289 (513; 24291)	3786 (111; 28865)	4380 (458; 59084)
C_{0h} (ng/mL)			
Mean (SD)	381 (320)	329 (357)	393 (391)
Median (Min; Max)	342 (33; 1879)	251 (2; 2276)	298 (2; 4852)

The impact of background protease inhibitor (PI) on etravirine exposure was a confounding factor in comparing pediatric etravirine exposures in TMC125-C126 and TMC125-C213 to those in adult pivotal trials (DUET-1 and DUET-2). Specifically, TMC125-C126 (pharmacokinetic study) used lopinavir/ritonavir (LPV/RTV) as capsule, tablet, and solution formulations in guiding pediatric dose matching. However, when different LPV/RTV formulations are given concomitantly with etravirine in adult subjects, there are differences in etravirine exposure. The LPV/RTV soft gel capsule formulation (no longer used in the U.S., but primarily used in TMC125-C126) increased etravirine exposures (Study TMC125-C122: AUC_{12h} 17%↑, Cmin 23%↑, and Cmax 15%↑). In contrast, LPV/RTV tablet formulation decreases etravirine exposures by 35%, 45%, and 30% for AUC_{12h}, Cmin and Cmax, respectively (Study TMC125-C197). It was not clear if LPV/RTV oral solution impacted etravirine PK.

Table 3 lists the distribution of various LPV/RTV formulations used in Studies TMC125-C213 and TMC125-C126. In Study TMC125-C126, LPV/RTV was the only protease inhibitor (PI) used in the study, though the formulation could not be confirmed in 50% (10/20) subjects at the 5.2 mg/kg dose. In Study TMC125-C213, 39% (39/101) of subjects were administered LPV/RTV as part of the optimized background regimen (OBR), 23 of which were administered tablets.

Table 3: Distribution of Kaletra formulations in Study TMC125-C213 and TMC125-C126

Kaletra formulation / Study	Tablets	Solution	Capsules	Ambiguous
TMC125-C213	59% (23/39)	18% (7/39)	13% (5/39)	10% (4/39)
TMC125-C126	10% (2/20)	15% (3/20)	25% (5/20)	50% (10/20)

The confounding impact of background PI on etravirine pediatric exposure was instead resolved by comparing etravirine exposures from a subset (52/101; 51 %) of pediatrics receiving DRV/RTV as part of the background regimen in TMC125-C213 to etravirine exposures observed in adult Phase 3 trials where all subjects received DRV/RTV as part of the background regimen. Table 4 shows the comparison of etravirine exposures in pediatric and adult subjects with DRV/RTV as background PI.

Table 4: Comparison of etravirine pediatric exposure and adult exposure with DRV/RTV as background PI

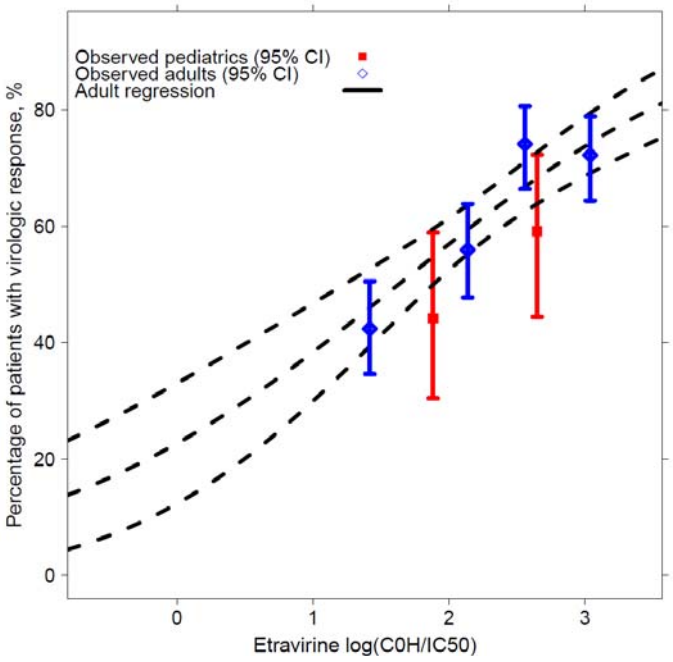
	Pediatrics (6 - <12 years)	Pediatrics (12 - <18 years)	Adults (DUET-1 and DUET-2)
N	21	31	575
AUC_{12h} (ng.h/mL) Mean (SD) Median (Min; Max)	 6202 (4791) 4791 (819; 24291)	 5088 (5239) 3822 (111; 28865)	 5506 (4710) 4380 (458; 59084)
C_{0h} (ng/mL) Mean (SD) Median (Min; Max)	 412 (406) 322 (47; 1879)	 336 (420) 253 (4; 2276)	 393 (391) 298 (2; 4852)

Etravirine exposures are comparable for pediatrics at the studied doses (median AUC_{12h}: 4487 ng.h/mL, all pediatrics) and adults (median AUC_{12h}: 4380 ng.h/mL) at approved dose when DRV/RTV was used as part of the background regimen. However, pediatric median etravirine AUC_{12h} is about 45 % lower when Kaletra tablets were part of the background regimen as compared with when DRV/RTV was part of the background regimen. It is not clear if this kind of difference exists for adult patients.

Question 2: Does the exposure-response (antiviral activity) relationship for etravirine support the proposed pediatric doses?

Yes. Exposure-response relationship for etravirine antiviral activity in pediatrics is comparable to that observed in adults and supports the proposed pediatric doses, as shown in Figure 1. Etravirine inhibitory quotient (IQ, C_{0h}/IC_{50}) was used instead of AUC_{12h} or C_{0h} in the analysis as the IQ accounts for exposure (C_{min}) and and resistance (IC_{50}) to etravirine. Comparable efficacy is expected between adult and pediatric populations as the exposure between adults and pediatrics was also comparable. Therefore, the proposed pediatric doses are appropriate.

Figure 1: Comparison of exposure-response relationship between pediatric subjects and adults at Week 24



Overall, the pediatrics etravirine exposure-response analysis trended towards higher virologic response in those patients with higher exposures (i.e., IQ, AUC_{12}, or C_{0h}).

Etravirine exposures are similar for children at the studied doses (5.2 mg/kg up to 200 mg b.i.d.) and adults at approved dose when DRV/RTV was coadministered. Likewise, the virologic response rate was similar between children (52%) and adults (60%) at Week 24 when DRV/RTV used in the OBR. The response rate is also comparable to outcomes observed in treatment-experienced pediatric trials with other ARVs.

The subgroup analysis indicated that etravirine exposures were lowest in pediatrics where the background PI was Kaletra tablets. Virologic response rate was slightly lower (than the response rate when DRV/RTV was in the background regimen) when Kaletra tablets were used in the background regimen (43%). However, no dose adjustments of etravirine will be recommended when etravirine is given to pediatric patients with Kaletra in the background regimen for the following reasons:

- Limited number of subjects in pediatric subgroup who received Kaletra tablets
- No dose adjustments for etravirine in combination with Kaletra in adults.
- Incomplete information related to the type of Kaletra formulation used in the trial

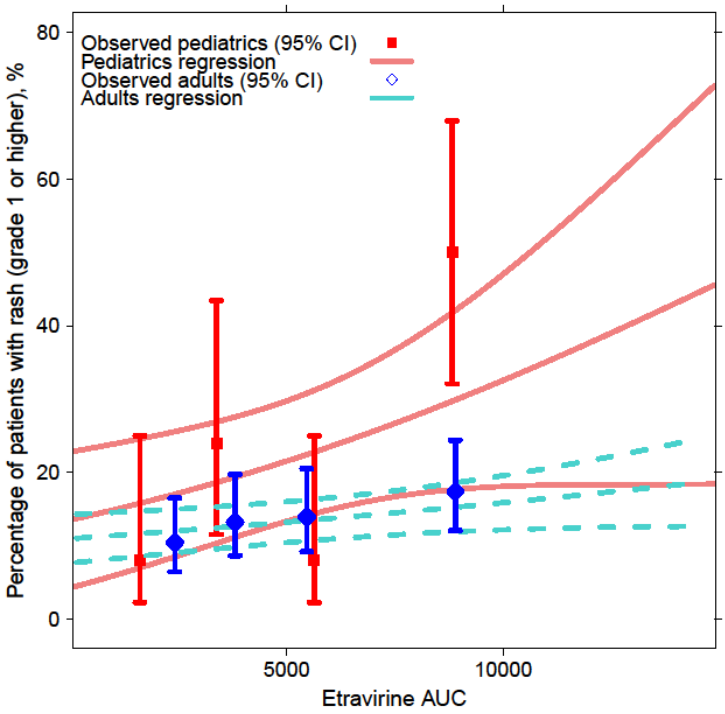
Question 3: Is the increased rash in pediatrics explained by demographics, exposure, or other covariates?

Yes. The overall incidence of rash was higher in the pediatric subjects than was observed in adults. This increased incidence of rash is mainly explained by a greater proportion of females in C213.

The frequency, type and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults, except for rash which was observed more frequently in Study TMC125-C213 than in the pivotal adult trials. Rash occurred in 23% (23/101) of pediatric subjects compared to 15% (91/599) of adults. Most often, rash adverse events were mild to moderate, and occurred within the second week of therapy. In addition, rash adverse events generally resolved within 1 week on continued therapy and infrequently led to treatment discontinuation (4% discontinuation due to rash).

Although etravirine exposures (AUC_{12h}) for children and adults overlap, children have a steeper exposure-rash relationship (Figure 2). This difference in the exposure-response relationship between adults and pediatrics indicates that factors other than exposure are contributing to the observed increase in rash adverse events from C213.

Figure 2: Rash vs AUC_{12h} Relationship for Adults and Pediatrics



One potential explanation for the increase in rash adverse events in the pediatric trials was that the pediatric trial had a larger proportion of female subjects (63%, 64/101) than adult trials (10%, 60/599). As shown in Table 5, previously analyses from the adult trials indicated that female patients were more likely to have rash adverse events than males. Taking a closer look at the rash events by gender from the pediatric trials, we observe that 27% (17/64) of females and 16% (6/37) of males experienced rash adverse events.

These rash adverse event rates by gender in the pediatric trial are comparable to the rash event rates by gender in the adult trials.

Table 5: Incidence of rash by gender in pediatrics and adults

		Pediatric (Study TMC125- C213)	Adult (Duets)
% of subjects with rash (number of subjects with rash/Total subjects)	Overall	23% (23/101)	15% (91/599)
	Male	16% (6/37)	14% (77/539)
	Female	27% (17/64)	23% (14/60)

Question 4: Did the etravirine inspections indicate that the quality of the pharmacokinetic evluations were acceptable?

Yes. Analytical and clinical site inspections were conducted by the Office of Scientific Investigations (OSI). The analytical site inspection has been completed and the applicant's responses to Form 483 were found to be acceptable. The inspection for the clinical site is pending and an amendment to the review will be submitted upon submission of the results.

The following issues were identified by the OSI and included in Form 483:

1. Failure to adequately validate the method to assay TMC125 during validation study BA790. Specifically:
   a. Freshly prepared quality controls (QCs) for run acceptance/rejection were not used for evaluation of long term stability (1185 days) of TMC125 in plasma.
   b. Failure to use freshly prepared calibrations and QC samples to evaluate processed sample stability of TMC125. Samples including calibrators and QC samples from precision and accuracy run 1 were reinjected.
2. Failure to use freshly prepared calibrators and QC samples to evaluate bench-top and freeze-thaw stability in validation study BA214 for assay of TMC125 in plasma.
3. Failure to track movement of study samples during studies TMC125-C126 and TMC125-C213 in that:
   a. Time of retrieval and return of subject samples during analysis were not documented in sample processing sheets.
   b. Failed to maintain freezer logs to record the removal and return of subject plasma samples.

To address the first two issues, the applicant repeated the stability assessment using freshly prepared calibration samples and QC samples. The results are shown in the following table.

Analyzing samples	Stability
Processed QC samples (PSS)	117 hours at room temperature (between +15ºC and +30º) 117 hours at refrigerator temperature (between +2ºC and +8ºC)
Spiked human heparin plasma	1 and 6 freeze/thaw cycles (thawing under normal light at room temperature) (between +15ºC and +30ºC) 48 hours at room temperature (normal light) (between +15ºC and +30º)
Long term stability in human heparin	1982 days in spiked plasma in a freezer (between -10ºC and -30ºC)

The maximum storage time and processing time are within the period of established stability.

Regarding the 3rd issue, the applicant implemented corrective actions to maintain freezer logs and documentation of sample movement, which is acceptable based on OSI assessment.

II. Detailed Labeling Recommendation

The label was updated by the applicant and the Agency. This section shows the clinical pharmacology related part of the label and the wordings in blue show the draft changes from the current approved label.

(b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

III. Detailed Pharmacometrics Review:

This section provides a detailed pharmacometrics review to determine if the applicant's proposed pediatric doses are appropriate.

A. Introduction

INTELENCE, co-administered with other antiretroviral (ARV) agents, is currently indicated for the treatment of HIV-1 infection in ARV treatment-experienced adult patients, including those with NNRTI resistance. The approved dosing regimen for adults is 200 mg taken twice daily orally following a meal.

The applicant is proposing to extend the indication to children and adolescents of 6 to less than 18 years based on data from two pediatric studies (TMC125-C126 (summary in Section IV) and TMC125-C213) and a population PK model report. This population PK model for etravirine (ETR) used richly sampled adult PK data from DUET-1 and DUET-2 (DUETs) trials as well as richly sampled pediatric PK data collected from Phase I pediatric study TMC125-C126. This model was further updated with sparsely sampled data from TMC125- C213 at the Week 12 analysis. A brief summary of TMC125-C213 is provided below.

TMC125 -C213:

Study Design: This ongoing Phase II, open-label study assesses the safety, tolerability, pharmacokinetics and antiviral activity of ETR during a 48-week treatment with ETR, when added to an investigator-selected optimized background regimen (OBR) comprising of a ritonavir (RTV)-boosted protease inhibitor (PI) (either lopinavir [LPV], darunavir [DRV], atazanavir [ATV] or saquinavir [SQV]) in combination with nucleos(t)ide reverse transcriptase inhibitor(s) (N[t]RTIs) in treatment-experienced human immunodeficiency virus – type 1 (HIV-1) infected pediatric subjects. Raltegravir (RAL) use was permitted as part of the OBR. The OBR had to contain at least 2 active antiretrovirals (ARVs). The additional use of enfuvirtide (ENF) was optional. ETR is administered with food and dosed per body weight, i.e. 5.2 mg/kg twice daily (b.i.d.) up to a maximum of 200 mg b.i.d. (the approved dose in adults). Because ETR is available only in tablet formulations (25-mg, 100-mg, and 200-mg), the doses were given as fixed doses based on the weight bands (Table 6).

Table 6: TMC125 doses for pediatric patients 6 to less than 18 years of age in Study TMC125-C213:

Weight	Dose
16 to < 20 kg	100 mg b.i.d.
20 to < 25 kg	125 mg b.i.d.
25 to < 30 kg	150 mg b.i.d.
≥ 30 kg	200 mg b.i.d.

About one hundred treatment-experienced, HIV-1 infected pediatric subjects between the ages of 6 and < 18 years, on a stable regimen with a confirmed HIV-1 plasma viral load ≥

500 copies/mL were included in the study. Subjects are treated for 48 weeks. The data and report submitted to the Agency described the results of primary pharmacokinetics and exposure-response relationship analysis of the ongoing trial when all subjects reached Week 24 or discontinued earlier. The cut-of date for the analysis was March 14, 2011.

Formulation:

	Batch Number(s)
TMC125 (25 mg, F066)	6GL41
TMC125 (100 mg, F060)	6A19 and 6IL9900

PK Sampling: At Week 24, 2 blood samples were taken. The first sample was a trough sample (taken immediately before intake of investigational medication). The second sample was to be taken at least 1 hour after intake of investigational medication. Sampling at Weeks 4, 8, 12 and 48 and at the Premature Withdrawal visit, if applicable, were done at any given time point after intake of medication except for the sample taken at Week 4, which had to be taken 4 hours after the intake of investigational medication.

Bioanalysis: Bioanalysis was performed by Johnson & Johnson Pharmaceutical Research & Development (J&JPRD), Turnhoutseweg 30B, 2340 Beerse, Belgium.
Plasma concentrations of TMC125 were determined using a validated liquid chromatography mass spectrometry/mass spectrometry (LC-MS/MS) method.

The standard curve and QC data indicated that the plasma assay method for TMC125 was precise and accurate as shown in the following table.

Table 7 Summary of Quality Control (QC) Results –Study TMC125-C213

Analyte	Linear range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Deviation)	QC samples (ng/mL)	Validation sample for stability and conditions
TMC125	2 – 5000 R^2> 0.999	≤ 8.2	-1.5 to 5.4	5. 34 (or 5.45), 111 (or 113), and 3820	Stable for at least 6 months at -70°C, and 3 freeze/thaw cycles

Reviewer's Note:
Bioanalytical inspection conducted by Office of Scientific Investigation (OSI) indicated that the stability of TMC125 was not evaluated using freshly prepared calibration samples and QC samples. The applicant repeated the assay as requested by the Agency. The results from the reassay indicated that the maximum storage time and processing time are within the period of established stability, which is acceptable. Please see the review conducted by Dr. Biswas from Office of Scientific Investigations for additional details.

B. Population Pharmacokinetic Analyses

Summary

The ETR pediatric dose was determined by matching pediatric exposures at the proposed doses to the adult exposure at the approved ETR dose (200 mg b.i.d.) and is supported by pediatric efficacy and safety data from C213.

Data

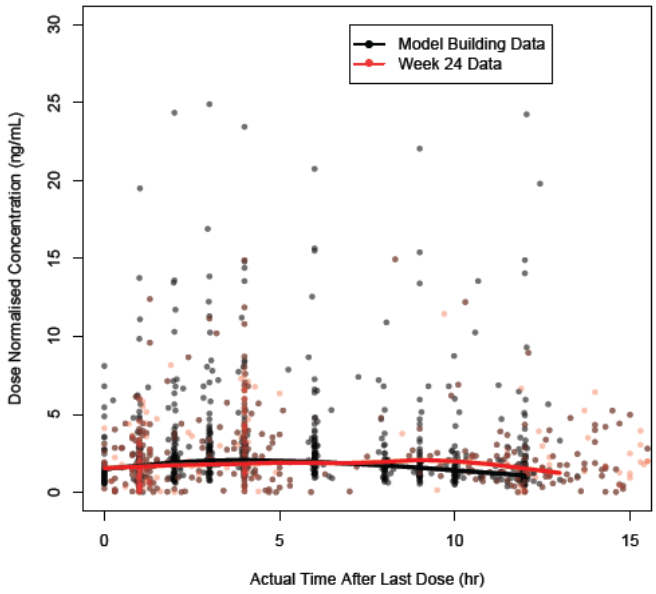
The data used for this analysis was obtained from subjects enrolled in study TMC125 - C213. A summary of the raw data is shown below in Table 8. A total of 1045 ETR plasma concentrations from 141 adult (richly sampled data from DUET trials) and pediatric (Study TMC125-C126 and sparse sampled data from Study TMC125-C213 at the Week 12 analysis) subjects were used for model building. A total of 467 plasma ETR concentration data at week 24 from 101 subjects in Study TMC 125-C213 were available for the individual PK analysis.

Table 8: Summary of Available Data

	Model Building Data	Week 24 Data
No. of Subjects	141	101
Dose (mg) BID	100,125,150,175,200	100,125,150,200
No. of Observations	1045	467
Assay LLOQ (ng/mL)	2.00	2.00
No. of Observations < LLOQ	30	50

Figure 3 shows the observed plasma ETR concentrations versus time after dose. This figure demonstrates that there was significant variability in plasma ETR concentration-time profiles between subjects. It also shows that plasma ETR concentrations were sampled around 1, 4 and 12 hours post-dose for the Week 24 Data, while the Model Building Data were sampled more uniformly across the dosing interval. Given this sampling distribution, it would be expected that individual estimates for parameters such as volume of distribution and absorption rate constant for pediatrics in C213 would be poor as a result of high ETA shrinkage.

Figure 3: Dose Normalized Observed Plasma ETR Concentrations versus Actual Time after Last Dose



The solid lines show the trend of the data with the density shaded dots representing the observed data. Darker colouring indicates multiple/overlapping observations.

During assembly of the NONMEM dataset, missing observations, and observations that were below the lower limit of assay quantification (LLOQ) were excluded from the dataset. Observations from unscheduled visits were also excluded from the dataset as dosing histories or date/time values were missing. In addition, observations were assumed to have arisen under steady-state conditions.

Outliers were defined as data points that appeared to be substantially outside that which would be considered normal for the given dataset and/or individual. However, as this was a Bayesian feedback analysis, all data, including outliers, were retained in the dataset. Covariates included in the graphical analysis were age, height (HT), body weight (WT), body mass index (BMI), creatinine clearance (CRCL), dose, sex and race.

Applicant's Analyses

The analysis was conducted using NONMEM version VII Level 1.0 and R 2.12.0. The Fortran compiler used was Intel Fortran Compiler XE for Mac OSX. The model used in this analysis was fitted to the data using the First Order Conditional Estimation (FOCE) method with the interaction option. For the empirical Bayes' estimation, MAXEVAL was set to zero.

The empirical Bayes' estimation was performed using a previously developed population model. This model consists of a sequential zero and first-order absorption process with a lag time and one-compartment disposition. The model was parameterized as lag time (ALAG1), zero order absorption (D1), first order absorption (KA), V/F and CL/F. Inter-individual variability was included on the parameters KA and CL/F. WT was included as a covariate effect on CL/F and Vc/F as presented in Equation 1 and Equation 2.. The residual error model was additive for the logarithmically transformed data, which is equivalent to

a proportional model for the non-transformed data. The final model parameter estimates are shown in Table 9.

$$\frac{CL}{F} = \left(\theta_1 \times \left(\frac{Weight}{70}\right)^{\theta_6}\right) \times exp(\eta_1) \quad (1)$$

$$\frac{Vc}{F} = \left(\theta_2 \times \left(\frac{Weight}{70}\right)^{\theta_7}\right) \quad (2)$$

Table 9 ETR PK Parameter Estimates

Parameter		Parameter Estimate	Parameter SE (CV%)	IIV estimate (CV%)	IIV SE (CV%)
CL/F (L/h)	θ_1	46.3	11	67.3	13
Vc/F (L)	θ_2	597	8.3		
KA (/h)	θ_3	1.07	34	174	34
D1 (h)	θ_4	2.42	19		
ALAG1 (h)	θ_5	0.335	47		
Influence of WT on CL/F	θ_6	0.273	55		
Influence of WT on Vc/F	θ_7	0.525	25		
Residual error Phase I (CV%)		30.7	2.0		

CL/F= apparent total clearance, Vc/F= apparent central volume of distribution, KA= first-order absorption rate constant, D1=duration of zero-order input, ALAG1=lag-time, SE=standard error, CV%=percent coefficient of variation

The individual Bayesian feedback parameters were used to obtain model derived estimates for AUC_{12h} and C_{0h} at steady state. The median value for a parameter over the different visits was determined if applicable (i.e. due to time varying covariates such as changes in body weight). A graphical covariate analysis was performed that relates the random effect on CL/F to age, weight, CRCL, sex, race and dose. For more details on the models and model building, refer to sponsor's population PK study report \\Cdsesub1\evsprod\NDA022187\0086\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\c213-pop-pk-w24\tmc125-c213-poppk-fd-0005.pdf

The Bayesian estimates of the ETR pharmacokinetic parameters (AUC_{12h} and C_{0h}) are summarized in Table 10. Graphical presentations (boxplots) of AUC_{12h} and C_{0h} for ETR are provided in Figure 4. ETR Cmax could not be reliably estimated using Bayesian feedback and was instead approximated for each individual using the median value of plasma ETR concentrations within 3-5 hours postdose (when available). Based on Table 9 and Figure 4, the applicant concludes that ETR exposures in children aged 6 to <12 years and adolescents were comparable to those in adults.

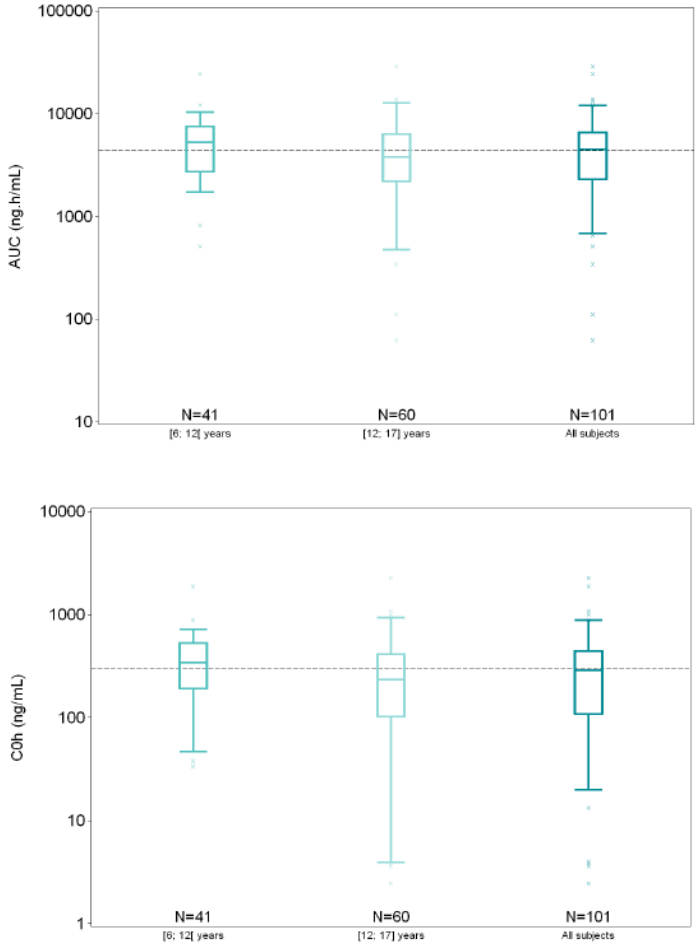
Table 10: Population Pharmacokinetic Estimates of ETR (Study TMC125-C213)

Pharmacokinetic Parameter	Children ≥ 6 to < 12 years N = 41	Adolescents ≥ 12 to < 18 years N = 60	All subjects N = 101
AUC_{12h} (ng.h/mL)			
n	41	60	101
Mean (SD)	5764 (4044)	4874 (4487)	5235 (4314)
Median (range)	5289 (513 - 24291)	3775 (62 - 28865)	4499 (62 - 28865)
C_{0h} (ng/mL)			
n	41	60	101
Mean (SD)	381 (321)	324 (357)	347 (342)
Median (range)	342 (33 - 1879)	236 (2 - 2276)	287 (2 - 2276)
C_{max} (ng/mL)			
n	28	38	66
Mean (SD)	673 (408)	527 (533)	589 (486)
Median (range)	671 (2 - 1620)	356 (13 - 2980)	466 (2 - 2980)

N = number of subjects; n = number of subjects with data

[a] ETR C_{max} was approximated for each individual using the median value of plasma ETR concentrations taken within 3-5 hours postdose, when available.

Figure 4: Boxplots of ETR Population Pharmacokinetic Parameters: AUC_{12h} (top) and C_{0h} (bottom) for pediatrics



Boxplots: median, 25th and 75th percentiles, 5th and 95th percentiles

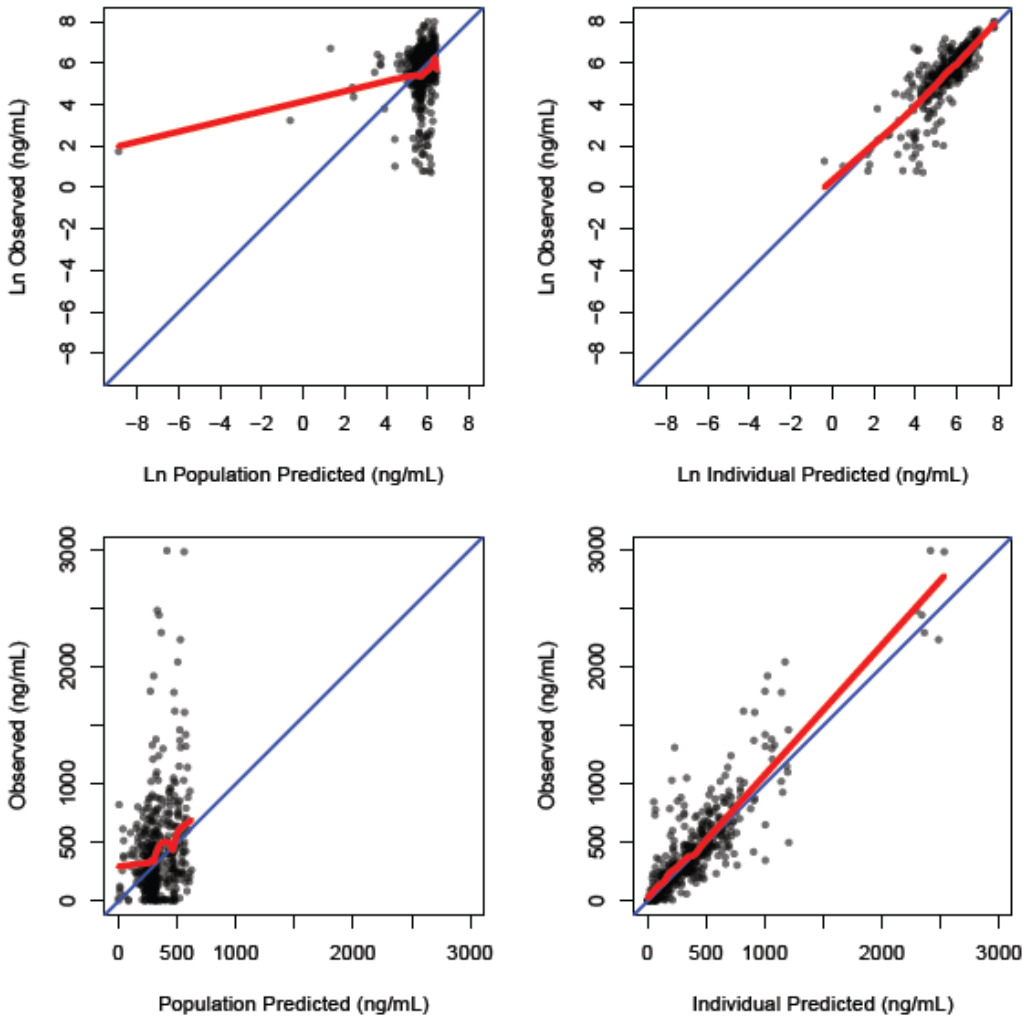
Reference line indicates median AUC_{12h} or C_{0h} in adults (DUET data; TMC125-C930 PK report, 18 December 2008)

A statistically significant effect on ETR exposure was observed for race (Asian versus Whites or Blacks), weight (as a continuous variable), age (as a continuous variable), and adherence to ETR based on pill count (as a continuous variable). A trend towards lower exposure to ETR was observed in Asians (median AUC_{12h} and C_{0h}: 2912 ng·h/mL and 154 ng/mL, respectively) relative to Black subjects (median 4661 ng·h/mL and 284 ng/mL, respectively) and White subjects (4844 ng·h/mL and 332 ng/mL, respectively). Higher exposures to ETR were observed in children versus adolescents and in subjects with lower weights. Higher exposures to ETR were also observed in subjects with higher adherence. Sex did not significantly influence the pharmacokinetics of ETR (AUC_{12h} or C_{0h}). The effect of background PI or PI formulation was not included in the applicant's analysis.

Reviewer's Assessment:

1. The individual exposures can be estimated with reasonable precision and minimal bias, although the effect of factors on CL/F may not be fully characterized. Specifically, the impact of factors such as background PI and PI formulation were not accounted for during the sponsor's analysis and despite including bodyweight in the population PK model there remained a trend between IIV CL/F estimates and body weight. However, the observed versus individual predicted plot in Figure 5 demonstrates reasonable precision and minimal bias, indicating that the individual AUC_{12h}, C_{0h} and $C_{ss;ave}$ can be reasonably estimated.

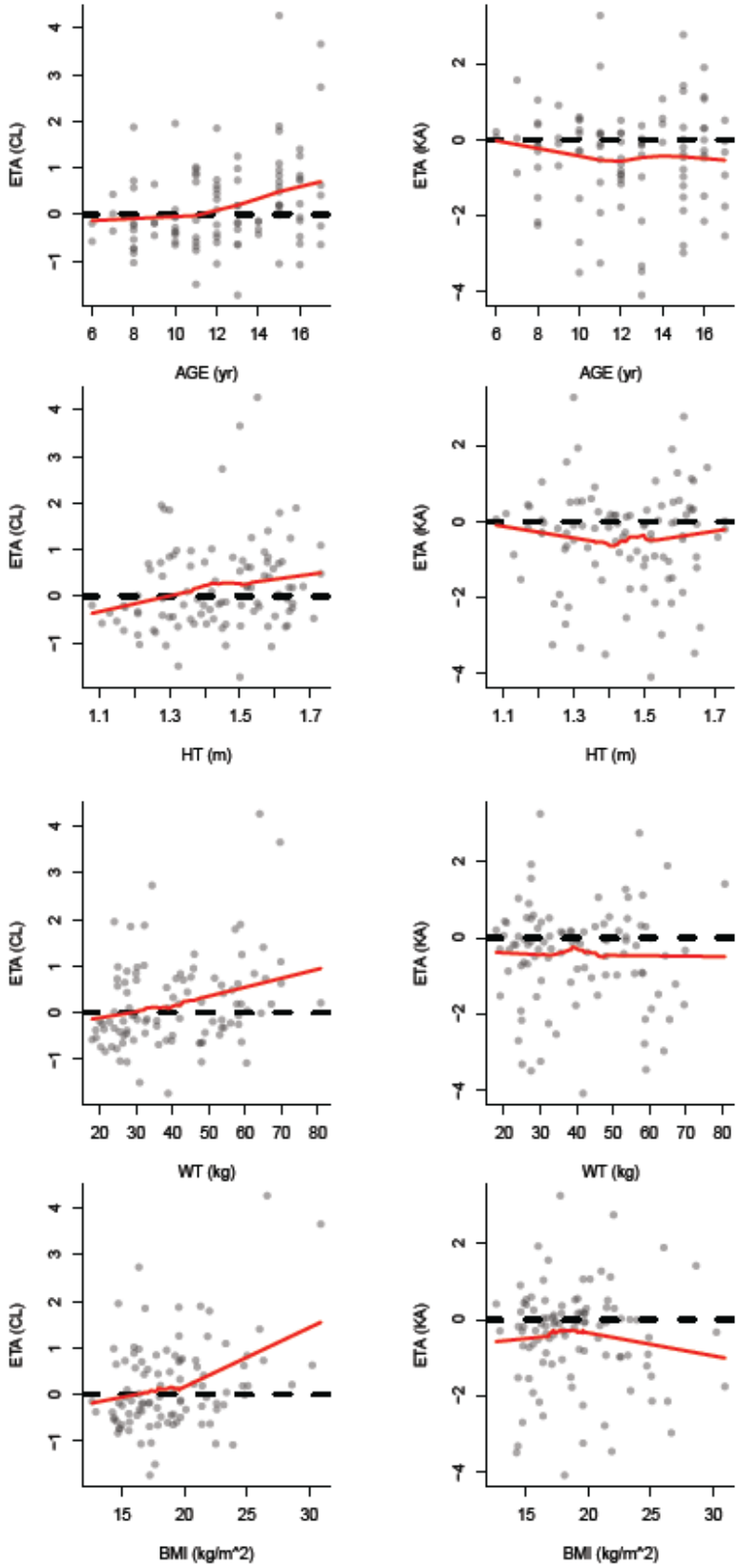
Figure 5: Goodness of Fit Plots - Observed versus Predicted



The blue solid line represents the line of unity with the solid red line representing a loess smooth of the data.

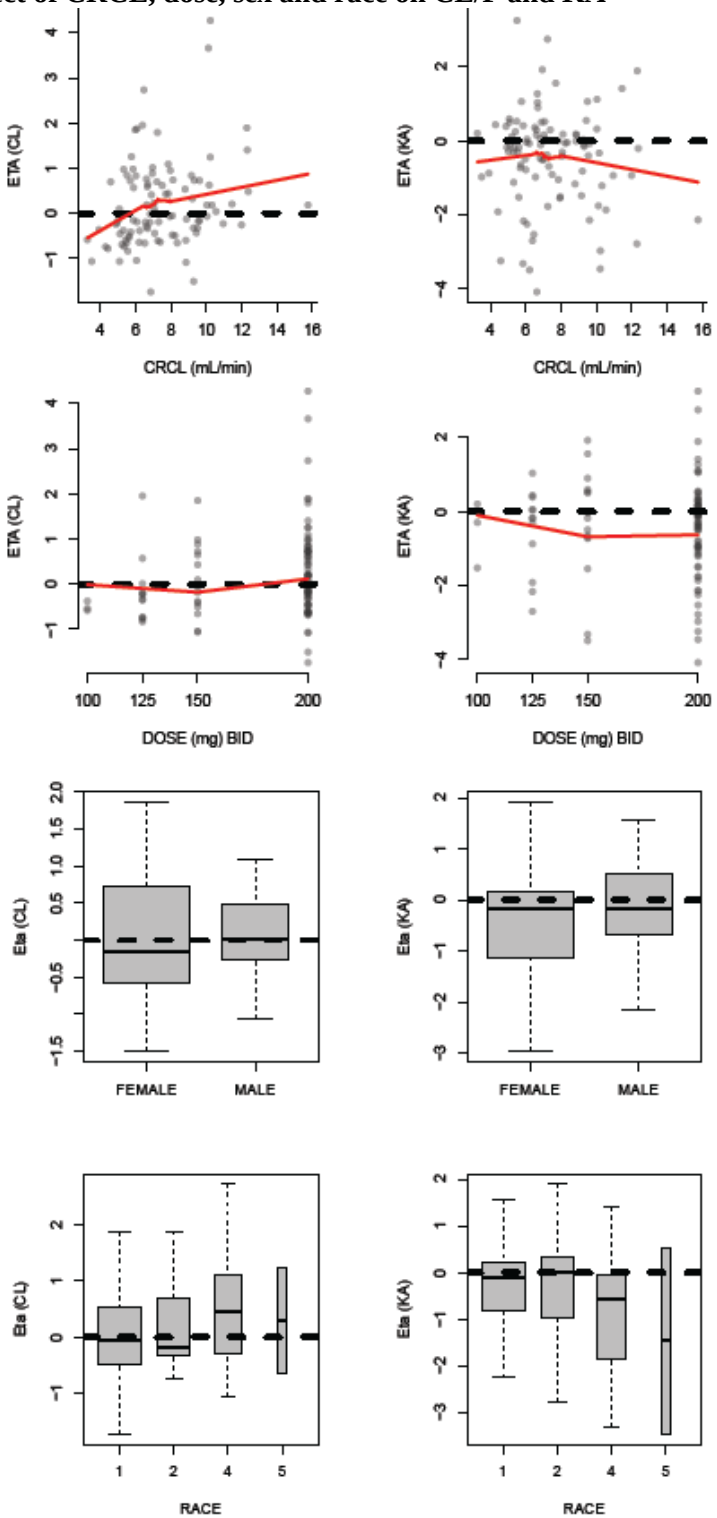
Plots of the individual random effects (labeled on the y-axis as ETA in the figure below) for CL/F and oral absorption rate (KA) against model covariates are shown below in Figures 6 and 7. The plots indicate that body size descriptors (i.e., height, weight, body mass index) together with creatinine and sex may explain a certain part of the variability in CL/F. No relationship between any of the covariates and oral absorption rate. Given body weight is already in the model, we recommend re-estimation of the covariate effect of body weight on CL/F when applying the model in subsequent pediatric populations.

Figure 6: Effect of age, height, body weight, and body mass index (BMI) on CL/F and KA



The red line is a loess smooth with observed data density shaded. Darker colouring indicates multiple/overlapping observations.

Figure 7: Effect of CRCL, dose, sex and race on CL/F and KA



The red line is a loess smooth with observed data density shaded. Darker colouring indicates multiple/overlapping observations.For RACE, 1=White, 2=Black, 4=Asian and 5=Unknown

2. The [redacted] (b) (4) dose of 5.2 mg/kg up to 200 mg b.i.d. in pediatrics provides comparable exposure to the adults at the approved dose of 200 mg b.i.d., as shown in the

applicant's analyses (Table 10 and Figure 4). This was further explored in the reviewer's analysis presented above (Table 2 and Table 4), also accounting for background PI.

3. ETR concentrations tend to be higher for subjects with Kaletra capsule formulation (LPV_capsules) as compared to Kaletra tablets (LPV_tablets), with Kaletra solution (LPV solution) in between. ETR AUC_{12h} was similar when DRV/RTV used as the coadministered PI or Kaletra solution used as the coadministered PI. This relationship is further evaluated in the reviewer's analysis.

The impact of background protease inhibitor (PI) on ETR exposure was not evaluated by the applicant and was investigated by the Agency for pediatric studies TMC125-C126 and TMC125-C213. Specifically, the pediatric studies permitted comparisons of the impact of darunavir/ritonavir (DRV/RTV), and lopinavir/ritonavir (LPV/RTV) as capsule, tablet, and solution formulations on etravirine (ETR) exposure. Of note, both pivotal efficacy studies in adults used darunavir/ritonavir (DRV/RTV) in the optimized background regimen (OBR).

In the Phase I pediatric study TMC125-C126, LPV/RTV (Kaletra) was used as part of the background regimen; however, Study TMC125-C213 included about 51% (52/101) of pediatric subjects using DRV/RTV as part of their OBR and about 39% (39/101) using Kaletra as part of their OBR. In addition, Kaletra was available in several pharmaceutical formulations for both studies: 133/33-mg soft-elastic capsule, 100/25-mg melt-extrusion tablet, 200/50-mg melt-extrusion tablet and 80/20 mg/mL oral solution. In some countries including United States, the recently approved melt-extrusion tablet formulation has replaced the soft-elastic capsule formulation.

The effect of Kaletra formulation on ETR exposures was evaluated because the older Kaletra soft gel capsule formulation increased ETR exposures (drug-drug interaction study TMC125-C122: AUC_{12h} 17%↑, C_{min} 23%↑, and C_{max} 15%↑). However, the Kaletra tablet formulation decreases ETR exposures by 35%, 45%, and 30% for AUC_{12h}, C_{min} and C_{max}, respectively (drug-drug interaction study TMC125-C197). The magnitude of Kaletra effect with the tablet formulation is comparable to the effect of DRV/RTV on ETR. The DRV/RTV drug-drug interaction study with ETR (TMC125-C176) demonstrated that coadministration with DRV/RTV reduced ETR AUC_{12h}, C_{min}, and C_{max} by 37%, 49%, and 32%, respectively. It was not clear if Kaletra oral solution impacted ETR PK.

The ETR-Kaletra DDI studies (TMC125-C122 and TMC125-C197) also used different ETR formulations. The applicant indicated that the results of these studies may have been influenced by the change in ETR formulation. However, ETR drug-drug interaction studies with DRV/RTV using different ETR formulations resulted in the comparable magnitude of impact of DRV/RTV on ETR exposures. Therefore, it is possible that Kaletra formulation was the major factor contributing to the difference in results of two ETR-Kaletra drug-drug interaction studies.

We assessed the ETR PK exposure for pediatrics whose Kaletra formulation was documented in Studies TMC125-C126 and TMC125-213 and compared their exposures

to those in adults (who received ETR with DRV/rtv). Table 3 lists the distribution of various Kaletra formulations used in Studies TMC125-C213 and TMC125-C126. In Study TMC125-C126, Kaletra was the only protease inhibitor (PI) used in the study. In Study TMC125-C213, about 51% of the children took DRV/RTV (52 out of 101). For 39 subjects who took Kaletra as the coadministered PI, most of the children took Kaletra tablets (64%).

Table 3: Distribution of Kaletra formulations in Study TMC125-C213 and TMC125-C126

Kaletra formulation / Study	Tablets	Solution	Capsules	Ambiguous
TMC125-C213	59% (23/39)	18% (7/39)	13% (5/39)	10% (4/39)
TMC125-C126	10% (2/20)	15% (3/20)	25% (5/20)	50% (10/20)

Figure 8 shows that ETR AUC_{12h} was mostly in the range of what was observed in the adults at the approved dose, referenced by the 1st and 3rd quartiles. Figure 9 compares cumulative frequency of AUC_{12h} in pediatrics (TMC125-C213) and in adults (DUETs). Both figures show ETR AUC_{12h} was comparable when DRV/RTV was used as the coadministered PI. ETR concentrations tend to be lower for subjects administered ETR with Kaletra tablets (LPV_tablets) compared to Kaletra capsule formulation, Kaletra solution, or DRV/RTV as PI. It is not clear if this kind of difference is also existed for adult patients. A cumulative distribution of pediatric and adult AUCs is shown in Figure 9. These results, likewise, demonstrate similar exposure at the median and upper quartile between adults and pediatrics administered DRV/RTV. There is separation between pediatrics and adults at the lower quartile, however, this separation is likely due to poor adherence in children.

Figure 8: Box plot for ETR AUC (at 5.2 mg/kg up to 200 mg b.i.d.) when Different PIs were used as part of OBR in Combined Studies TMC125-C213 and TMC125-C126 (stage II)

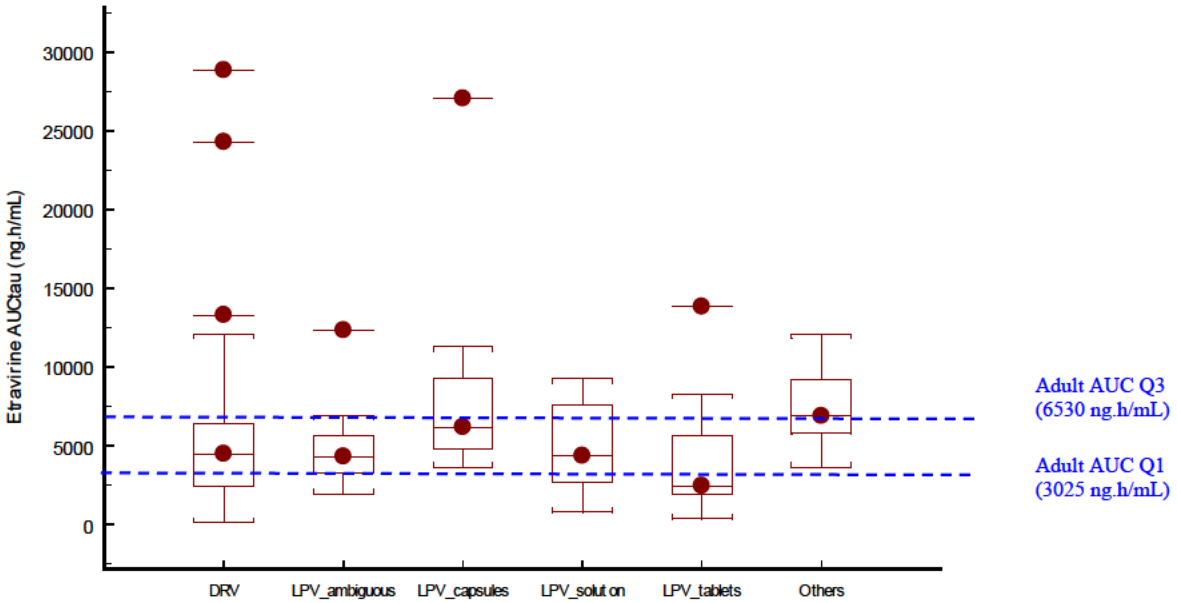
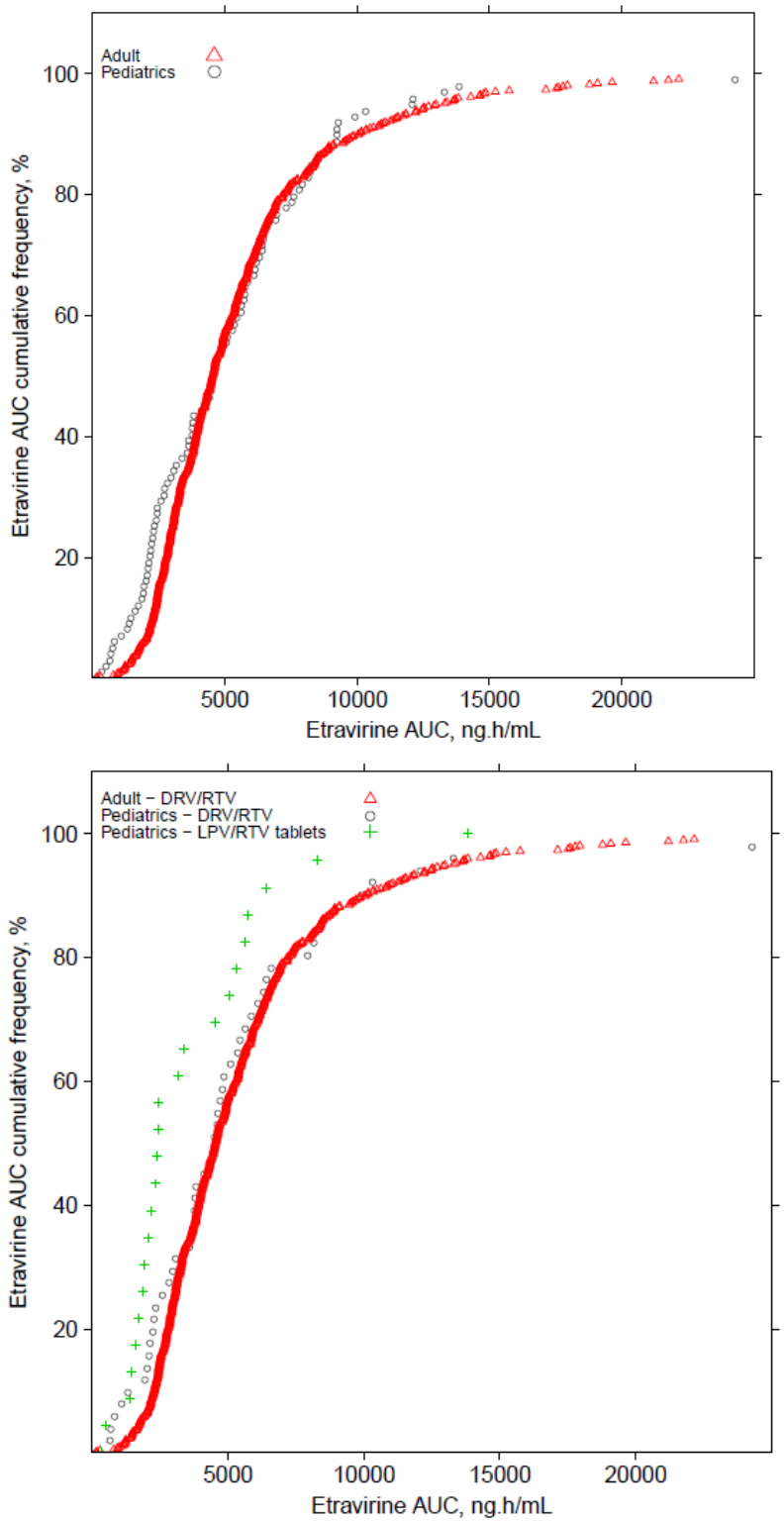
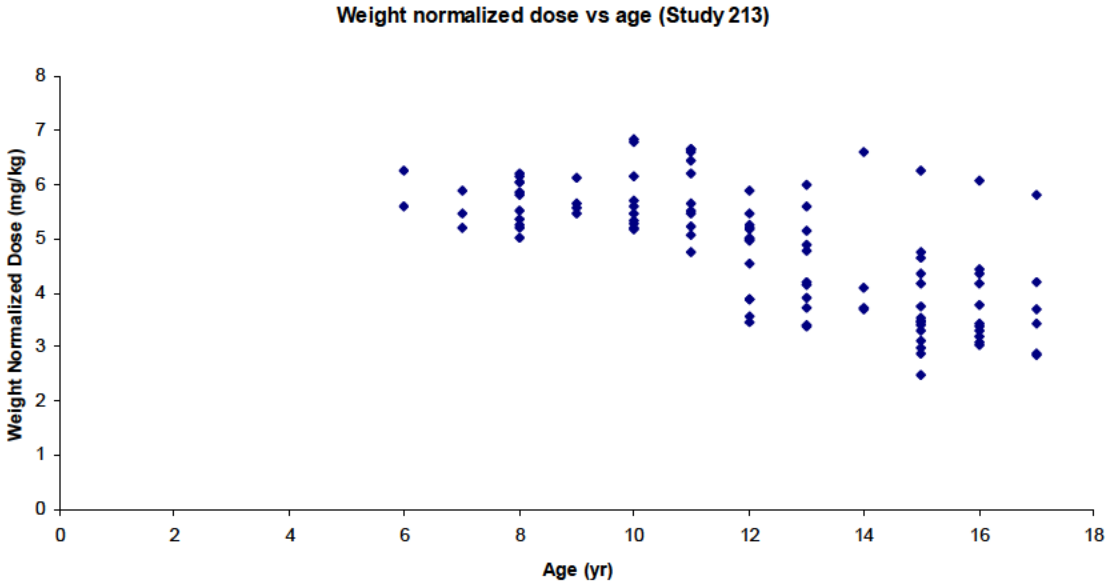


Figure 9: Cumulative frequency of AUC_{12h} comparison between pediatrics (TMC125-C213) and adults (DUETs). Top panel: all pediatrics were compared to adults; Bottom panel: subjects coadministered ETR with Kaletra <u>tablets</u> were compared to adults and pediatrics coadministered ETR with DRV/RTV



4. Although the exposure tends to be higher for children 6 to <12 years of age as compared to adolescents, the exposures in both groups are within the range of the observed values in adults at the approved 200 mg bid dose. Adolescents generally received a lower weight normalized dose with most of the adolescents (93.3%) using the maximum dose of ETR (200 mg b.i.d.) as shown in Figure 10.

Figure 10: Weight Normalized Dose vs. Age



As shown in Figure 11, weight normalized CL/F is similar over the pediatric age range evaluated in C213. Therefore, lower weight normalized doses for adolescents would result in a lower exposure as compared to younger children. However, the background PI/formulation was a confounding factor. There was higher percentage of subjects who received ETR with Kaletra tablets in adolescents (26%) than in younger children (17%) in Study TMC125-C213. Overall, the ETR exposures in adolescents are still generally within the range of the observed adult values at the approved 200 mg b.i.d., using quartile 1 and quartile 3 as references (Figure 12). In Study TMC125-C126, because there was limited number of subjects in each age group, large variability was observed. The doses used in Study C213 and Study TMC125-C126 Stage II were same as the proposed dose, except for children with the body weight between 30 kg and 35 kg, where 175 mg b.i.d. were used in Study C126 Stage II instead of 200 mg b.i.d.. Figure 9 compares cumulative frequency of AUC_{12h} in pediatrics (TMC125-C213, pink dots) and in adults (DUETs, green dots). It shows that two curves are generally overlapping, except that more pediatric subjects have lower exposure, probably due to poor adherence in children.

Figure 11: ETR Apparent Clearance vs. Age

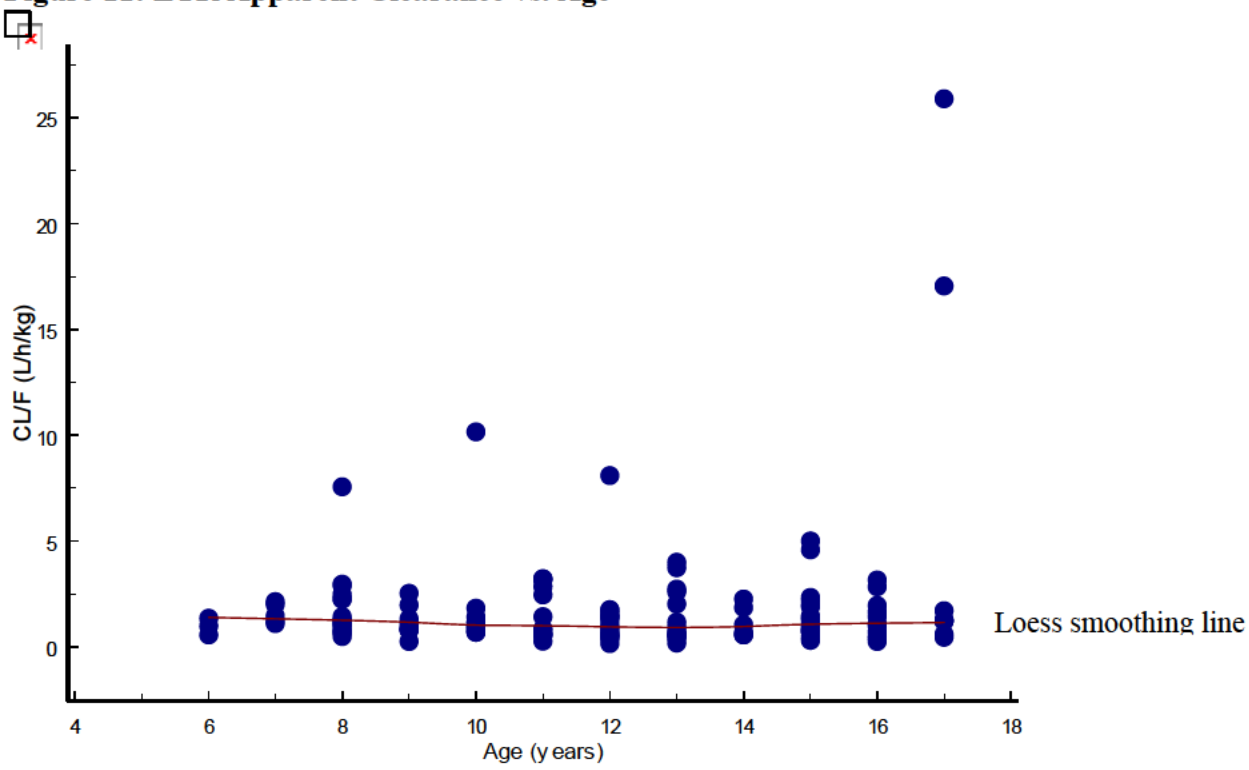
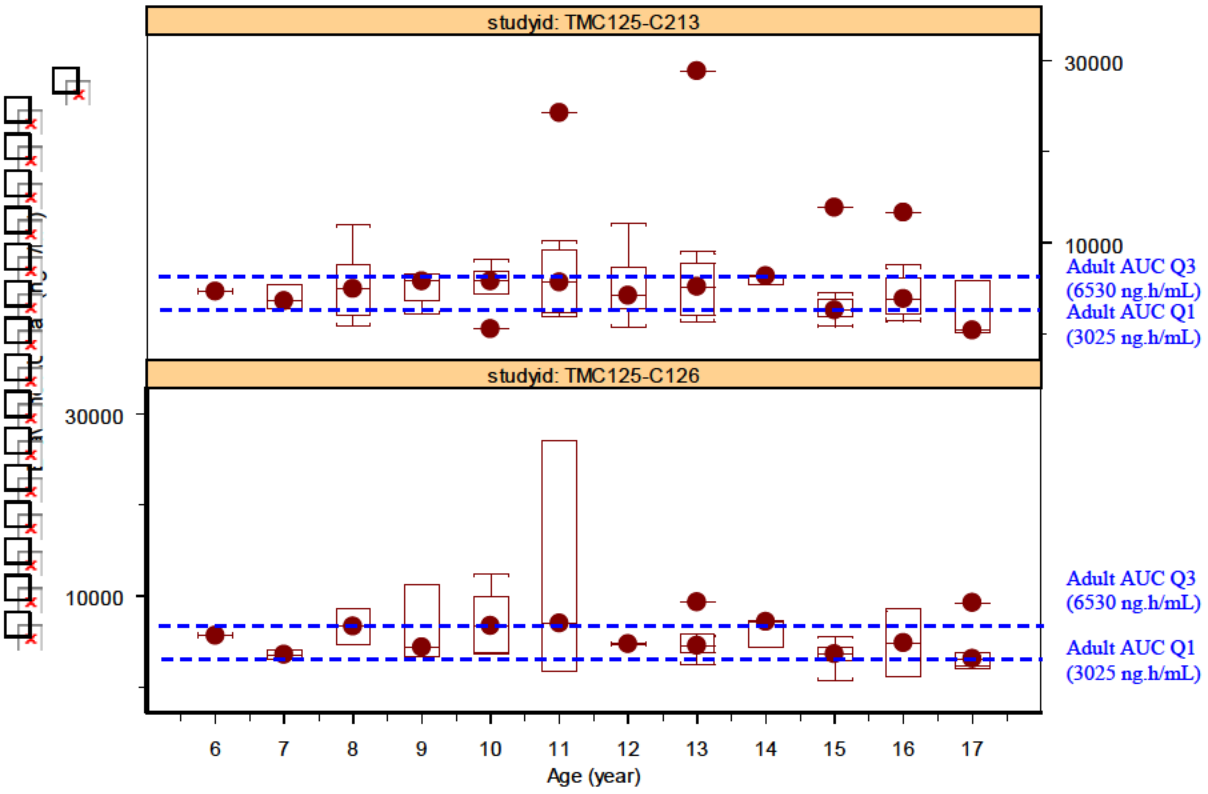


Figure 12: Box plots for ETR AUC_{12h} vs. Age in Studies TMC125-C213 and TMC125-C126 (stage II) at 5.2 mg/kg up to 200 mg b.i.d.



C. Exposure-response Analysis: Virologic Success

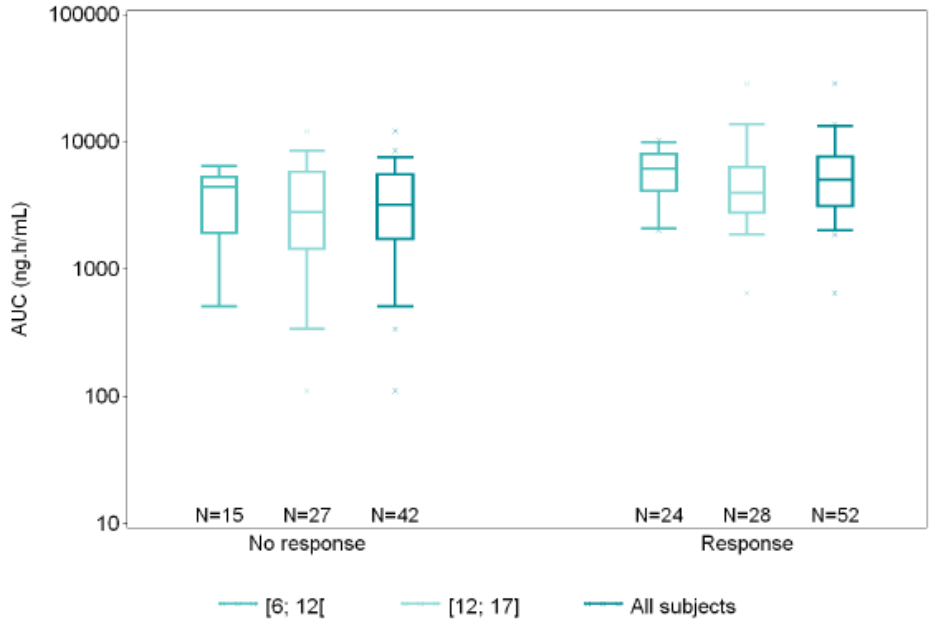
Summary

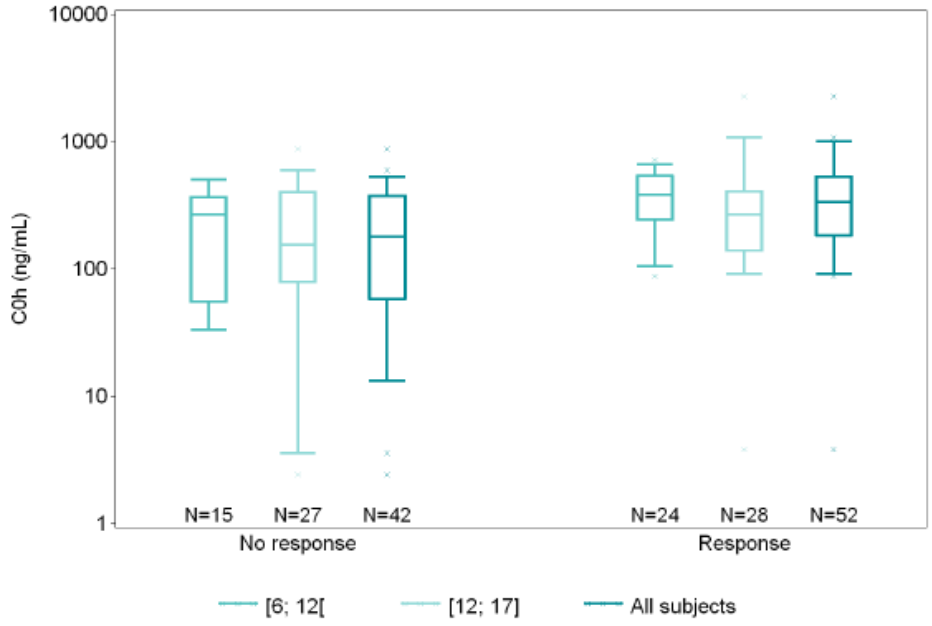
The ad hoc analysis indicated that ETR exposure-antiviral activity relationship is comparable between children and adults. Therefore, if the exposure is matching between children and adults, comparable efficacy is expected between these two populations.

Applicant's Analyses

Box plots of ETR pharmacokinetic parameters AUC_{12h} and C_{0h} versus responders and non-responders (responder is subject whose virologic response< 50 copies/mL at Week 24) at Week 24 is provided in Figure 13. The data show that ETR exposure tends to be higher in the responders when compared with the non-responders.

Figure 13: Boxplots of ETR Pharmacokinetic Parameters by Virologic Response (< 50 Copies/mL) at Week 24: AUC_{12h} (Top) and C_{0h} (Bottom)

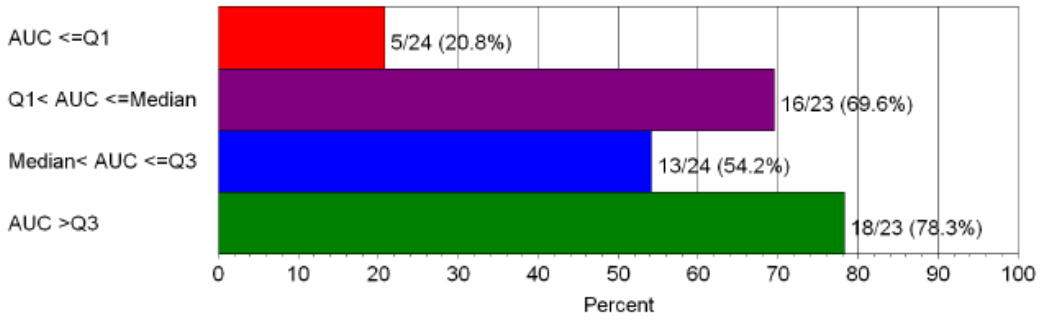




Boxplots: median, 25th and 75th percentiles, 5th and 95th percentiles

Figure 14 shows the percentage of subjects with virologic response (< 50 copies/mL) by AUC_{12h} quartiles, both at the Week 24 time point. For subjects in the lowest ETR AUC_{12h} quartile ($AUC_{12h} \leq 2308$ ng·h/mL), the virologic response rate (20.8%) at Week 24 was lower compared to subjects in higher ETR AUC_{12h} quartiles (range 54.2% to 78.3%; ad hoc analysis). Similar results were observed with C_{0h}.

Figure 14: Virologic Response (< 50 Copies/mL) by ETR AUC_{12h} Quartiles at Week 24



Q1 =2308 ng.h/mL, Median = 4487 ng.h/mL, Q3 = 6419 ng.h/mL

Reviewer's Assessment

Exposure-response relationship was explored using logistic regression. As shown in Figure 1 (Page 6), exposure-response relationships are comparable between pediatrics and adults. For both pediatrics and adults, virologic response rate is lower for subjects with AUC_{12h} less than Q1 (2308 ng.h/mL for pediatrics and 3025 ng.h/mL for adults), but exposure-response relationship become relatively flat at AUC_{12h} > Q1.

Subgroup virologic response was explored based on race, age, and background PI. However, because there are limited data for each subgroup and the limitation with sparse sampling, the exposure-efficacy relationship in children needs to be interpreted cautiously.

The subgroup analysis (Figure 8, Page 19) indicated that ETR exposures were highest when Kaletra capsule was coadministered, followed by DRV/RTV, Kaletra solution, and Kaletra tablet. ETR exposures are comparable for children at the studied doses and adults at approved dose when DRV/RTV was coadministered, which result in the comparable virologic response rate at Week 24 in children (52%) and adults (60%) when DRV/RTV used in the OBR (Table 11).

The subgroup analysis for exposure indicated that Asians had 40% and 38% lower AUC_{12h} compared to Whites and Blacks, respectively, confounded by the background PI and PI formulation. Whites and Blacks have similar exposures. However, Asians had similar virologic response rate as compared to Whites, and Black had lowest response rate (Table 10). The results are consistent with that observed in adults, although in adults, only very limited Asian subjects were included in clinical trials. There is no need to increase the dose for Asians based on the pediatric data.

The subgroup analysis also indicated that ETR AUC for children 12- <18 years of age was 29% lower than AUC for children 6- <12 years of age. This difference was reflected to the difference in virologic response rate, where virologic response rate was 11% lower for children 12- <18 years of age as compared to children 6- <12 years of age. The virologic response rate for children 12- <18 years of age (48%) is slightly lower than that in adults (52%, DUETs). However, because safety data were not sufficient for dose higher than 200 mg b.i.d., it is acceptable to cap the dose at 200 mg b.i.d. for adolescents.

Table 11: Virologic Response Rate by Subgroup Analyses

Subgroup	Race			Age		Coadministered PI/formulation			
	Asian	White	Black	6- <12 yrs	12- <18 yrs	DRV/RTV	Kaletra tablets	Kaletra solution	Kaletra capsules
Virologic Response Rate % (N of responder/total)	60% (12/20)	63% (31/49)	30% (9/30)	59% (24/41)	48% (29/60)	52% (27/52)	43% (10/23)	57% (4/7)	80% (4/5)

D. Exposure-response Analysis: Adverse Events (Rash)

Summary

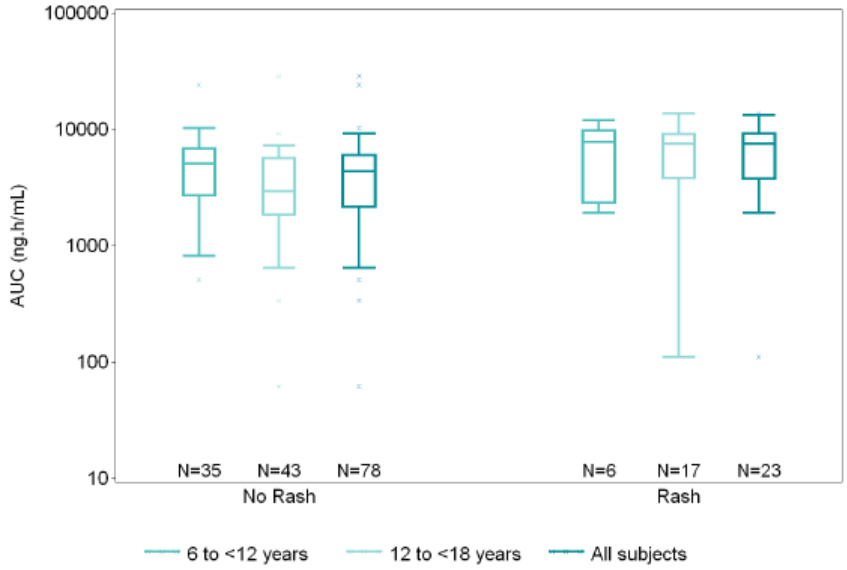
The frequency, type and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults, except for rash which was observed more frequently than in adults. Rash (≥ grade 2) occurred in 15% of pediatric subjects as compared to 10% in adults. Most often, rash was mild to moderate, and occurred in the second week of therapy. Rash was mostly self-limiting and generally resolved within 1 week on continued therapy. The discontinuation rate for rash was 4%.

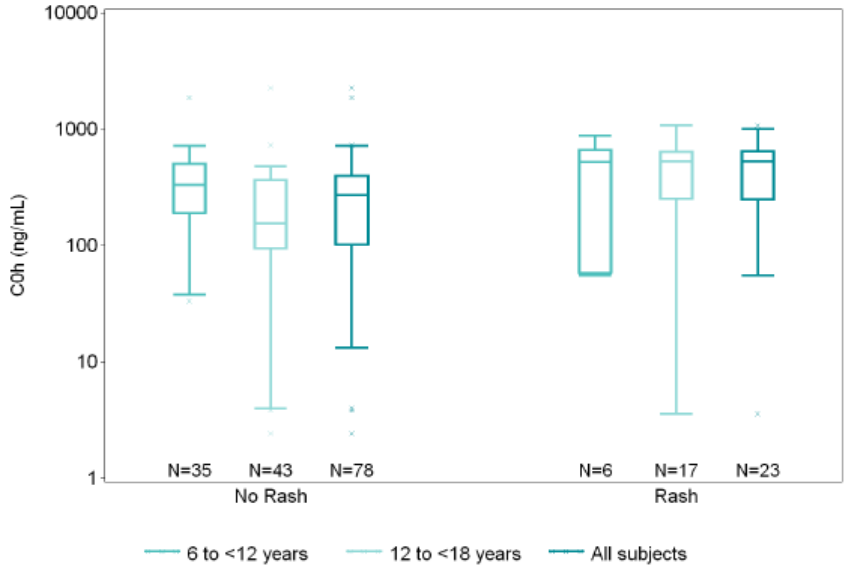
A greater frequency of rash events were observed in female subjects compared to male subjects, which is consistent with the observation in adults. Serious (grade 3 or 4) rash cases including events leading to discontinuations were observed in female subjects only.

Applicant's Analyses

Figure 15 shows the boxplots of ETR AUC_{12h} and C_{0h} by rash cases (no/yes). Figure 16 shows the percentage of subjects with rash cases by AUC_{12h} quartiles up to the cut-off date for the Week 24 analysis. A trend towards a higher incidence of rash cases in the highest ETR AUC_{12h} quartile (AUC > 6590 ng·h/mL) was observed.

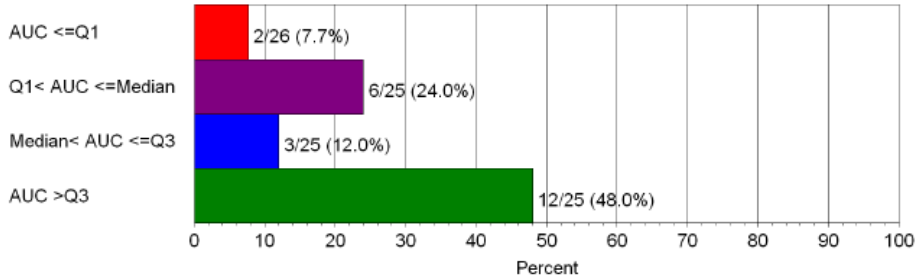
Figure 15: Boxplots of ETR Pharmacokinetic Parameters by Rash Cases (Grouped Term) (No/Yes): AUC12h (Above) and C0h (Below)





Boxplots: median, 25th and 75th percentiles, 5th and 95th percentiles

Figure 16: Frequency of Rash Cases (Grouped Term) by AUC12h Quartiles



Q1 = 2308 ng.h/mL, Median = 4499 ng.h/mL, Q3 = 6590 ng.h/mL

Subgroup analysis of rash cases by sex was conducted for children as a sex difference for the incidence of rash with ETR was previously seen in the adult Phase III DUET studies. By sex, 17 (26.6%) females and 6 (16.2%) males were reported with rash cases. In the pooled DUET studies, rash occurred in 23% (14/60) of females and 14% (77/539) of males.

An ad hoc multivariate logistic regression model was used to identify potential prognostic factors for the development of rash. This model included several factors as shown in Table 12. This analysis was performed for exploratory purposes only. Results should be interpreted with caution as sample sizes within the subgroups were small.

The specific PI used in the OBR was the only factor that was identified as a potential independent predictor of rash ($p < 0.05$) by the final multivariate model. Indeed, rash appeared to occur less frequently in subjects using LPV/RTV in the OBR (3 out of 39 subjects or 7.8%) compared to subjects using DRV/RTV (15 out of 52 or 28.9%) or another boosted PI (5 out of 10 or 50%; Other factors that appeared to be weaker predictors of rash were baseline CD4 cell count and age ($0.05 < p < 0.10$), with the incidence of rash increasing with increased baseline CD4 cell count and age.

Table 12: Univariate and Multivariate Logistic Regression Model for Rash

Parameter	Type 3 p-value
Univariate modeling[a]	
Age	**0.0814**
ETR AUC_{12h}	**0.0275**
z-score for BMI	0.2439
Combined use of DRV/rtv and RAL (Yes/No)	0.5600
Adherence (by pill count)	0.4452
Tanner stage (genitalia/breasts)	0.3988
Baseline CD4 cell count (bCD4)	**0.0348**
Baseline $\log_{10}$ viral load (bVL)	0.2735
PI used in initial therapy (DRV/LPV/Other)	**0.0027**
Tanner stage (pubic hair)	0.2893
Race	**0.0736**
RAL used in OBR (Yes/No)	0.6939
Sex	0.2235
Multivariate modeling[b]	
Age AUC bCD4 PI **Race**	0.1911
Age **AUC** bCD4 PI	0.1285
Age bCD4 PI	0.0940
bCD4 PI	0.0754
Final Multivariate Model	
PI	0.0027

[a] Factors with a p-value < 0.15 from the univariate model were considered for further evaluation in the multivariate model.

[b] Backwards elimination of factor with highest p-value until all remaining factors have a p-value < 0.05.

Reviewer's Assessment

Additional analyses were conducted to compare the exposure-rash relationship between pediatrics and adults. Figure 2 (Page 7) indicates that although AUCs for children and adults overlap, pediatrics have a steeper exposure-rash relationship, which suggested that

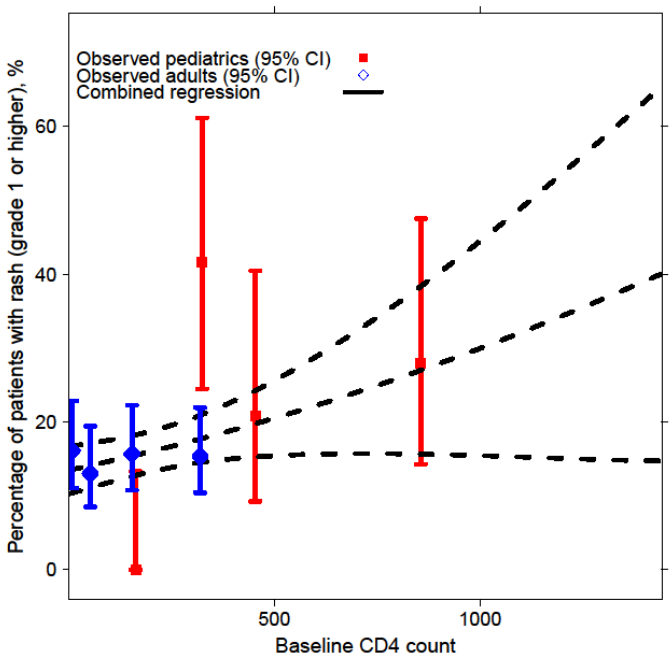
factors beyond exposure are contributing to the observed increase incidence of rash in pediatrics.

The applicant's analysis indicated that females had a higher rash rate as compared to males. In pediatrics, 17 (27%) females and 6 (16%) males were reported with rash cases, which is comparable to the results observed in the adult DUET studies (rash occurred in 23% of females and 14% of males). However, the pediatric trial (C213) had a larger proportion of female subjects (63%) than adult trials (10%), which could explain a portion of the increase in adverse event rate for the overall trial.

The applicant's analysis indicated rash appeared to occur less frequently in subjects using LPV/RTV in the OBR (3 out of 39 subjects or 7.8%) compared to subjects using DRV/RTV (15 out of 52 or 28.9%) or another boosted PI (5 out of 10 or 50%). However, because all the subjects in the adult DUET studies used DRV/RTV as coadministered PI, PI difference can not explain the higher rash rate in children than in adults.

The applicant's analysis indicated that baseline CD4 cell count and age appeared to be weaker predictors for rash ($0.05 < p < 0.10$), with the incidence of rash increasing with increased baseline CD4 cell count and age. Baseline CD4 cell count was associated with rash for another NNRTI, nevirapine. Therefore, rash vs baseline CD4 cell count relationship was further explored using logistic regression. Figure 17 shows that rash versus baseline CD4 cell count relationship for adults was flat, while there is a trend of increased rash with baseline CD4 cell count in pediatircs. However, baseline CD4+ counts had little overlap between the two trials. In addition, CD4+ was overall higher in females than in males in both the adult and pediatric trials, confounding interpretation of these results as sex was already identified as a factor in incidence of rash.

Figure 17: Rash vs Baseline CD4 cell count Relationship for Adults and Pediatrics



In conclusion, the major factor for the higher incidence of rash in the pediatric trial was the inclusion of a higher proportion of females compared to the subjects enrolled in the adult trials.

IV. Individual Review for TMC125 -C126:

A Phase I, open-label trial to investigate pharmacokinetics, safety and tolerability of TMC125 at steady-state in treatment-experienced HIV-1 infected children.

Objectives:

- To obtain steady-state pharmacokinetics and dose recommendations per body weight of TMC125 (b.i.d.) in treatment-experienced HIV-1 infected children ≥ 6 years old and weighing ≥ 20 kg.
- To evaluate short-term safety and tolerability of TMC125 b.i.d. in treatment-experienced HIV-1 infected children.

Study Design: This was a Phase I, open-label trial to evaluate the steady-state pharmacokinetics and short-term safety and tolerability of TMC125 at 2 different dose levels (i.e., 4 mg/kg twice daily [b.i.d.] in Stage 1 and 5.2 mg/kg b.i.d. in Stage 2). The trial population consisted of treatment-experienced HIV-1 infected children and adolescents who were virologically suppressed on a stable antiretroviral (ARV) regimen including lopinavir/ritonavir (LPV/rtv) and a minimum of 2 nucleoside reverse transcriptase inhibitors (NRTIs), with or without enfuvirtide (ENF).

In Stage 1, about 10 subjects were included per age group (Group 1: ≥ 6 to < 12 years old and Group 2: ≥ 12 to ≤17 years old). All subjects received TMC125 4 mg/kg b.i.d. (Table 13) for 7 days, with an additional morning dose on Day 8.

Table 13: Dose 4 mg/kg b.i.d. in Stage 1, Study TMC125-C126

Weight (kg)	Dose	Tablets
20 to 24.9	100 mg b.i.d.	4 x 25 mg b.i.d. or 1 x 100 mg b.i.d.
25 to 34.9	125 mg b.i.d.	5 x 25 mg b.i.d. or 1 x 100 mg b.i.d. + 1 x 25mg b.i.d.
35 to 39.9	150 mg b.i.d.	6 x 25 mg b.i.d. or 1 x 100 mg b.i.d. + 2 x 25 mg b.i.d.
40 to 44.9	175 mg b.i.d.	7 x 25 mg b.i.d. or 1 x 100 mg b.i.d. + 3 x 25 mg b.i.d.
≥ 45	200 mg b.i.d.	2 x 100 mg b.i.d. or 8 x 25 mg b.i.d.

In Stage 2, about 10 subjects per age group were included. All subjects received TMC125 5.2 mg/kg b.i.d. (Table 14) for 7 days, with an additional morning dose on Day 8.

Table 14: Dose 5.2 mg/kg b.i.d. in Stage 2, Study TMC125-C126

Weight (kg)	Dose[a]	Tablets
20 to 24.9	125 mg b.i.d.	5 x 25 mg b.i.d. or 1 x 100 mg b.i.d. + 1 x 25mg b.i.d.
25 to 29.9	150 mg b.i.d.	6 x 25 mg b.i.d. or 1 x 100 mg b.i.d.+ 2 x 25 mg b.i.d.
30 to 34.9	175 mg b.i.d.	7 x 25 mg b.i.d. or 1 x 100 mg b.i.d. + 3 x 25 mg b.i.d.
≥ 35	200 mg b.i.d.	2 x 100 mg b.i.d. or 8 x 25 mg b.i.d.

All subjects received TMC125 b.i.d. given in combination with a stable ARV regimen that comprised of LPV/rtv in combination with at least 2 NRTIs, with or without ENF, at approved pediatric doses.

Subjects were required to take the study medication orally with 50 to 200 mL of water, within 10 minutes after completion of a standard meal.

Formulation:

	Batch Number(s)
TMC125 (25 mg, F066)	6GL41
TMC125 (100 mg, F060)	6A19 and 6IL9900

Pharmacokinetic Sampling:
In both stages, 12-hour pharmacokinetic sampling was performed on Day 8 of the treatment period with samples taken predose, and 1, 2, 3, 4, 6, 8, 10, and 12 hours postdose.

Bioanalysis:
Bioanalysis was performed by Johnson & Johnson Pharmaceutical Research & Development (J&JPRD), Turnhoutseweg 30B, 2340 Beerse, Belgium.
Plasma concentrations of TMC125 were determined using a validated liquid chromatography mass spectrometry/mass spectrometry (LC-MS/MS) method.

The standard curve and QC data indicated that the plasma assay method for TMC125 was precise and accurate as shown in the following table. However, the bioanalytical inspection conducted by Office of Scientific Investigation (OSI) indicated that the stability of TMC125 was not evaluated using freshly prepared calibration samples and QC samples. The applicant repeated the assay as requested by the Agency. The results from the reassay indicated that the maximum storage time and processing time are within the period of established stability, which is acceptable. Please see the review conducted by Dr. Biswas from Office of Scientific Investigations for additional details.

Table 15: Summary of Quality Control (QC) Results --- TMC125- C126

Analyte	Linear range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Deviation)	QC samples (ng/mL)	Validation sample for stability and conditions
TMC125	2 – 5000 R^2> 0.987	≤ 7.0	-3.7 to 4.7	5. 5, 110, and 3800	Stable for at least 6 months at -70°C, and 3 freeze/thaw cycles

Pharmacokinetic Results:

A summary list of key pharmacokinetic parameters of TMC125 for Stage 1 and 2 are presented in Table 16 below. In Stage 1 and 2, a substantial deviation around the mean was noticed for the youngest age group and inter subject variability (%CV) for C_{min}, C_{max}, $C_{ss,av}$ and AUC_{12h} ranged from 101-106% and 90-97% for Stage 1 and Stage 2, respectively. However, this large variability was partly driven by 1 subject who participated in both stages and who had consistently high exposures at both 4 mg and 5.2 mg b.i.d. (subject number 126-0071 and 126-1072 in Stage 1 and Stage 2, respectively). When excluding this subject, the subject variability on the mentioned parameters ranged from 69-98% and 48-77% for Stage 1 and Stage 2, respectively

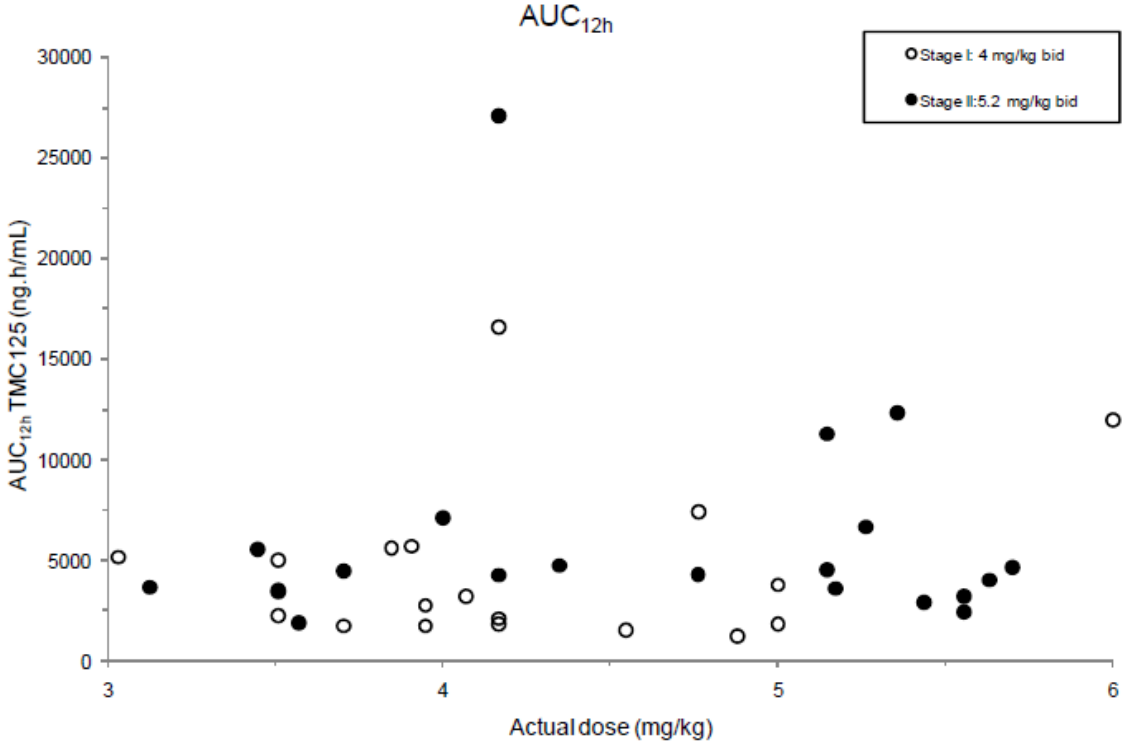
Table 16: Pharmacokinetic Results of TMC125 after Administration of TMC125 4 mg/kg b.i.d. (Stage 1) and After Administration of TMC125 5.2 mg/kg b.i.d. (Stage 2) --- Study TMC125-C126

Pharmacokinetics of TMC125 (mean ± SD, t_{max}: median [range])	4 mg/kg TMC125 b.i.d. children and adolescents (Stage 1)	5.2 mg/kg TMC125 b.i.d. children and adolescents (Stage 2)
n	19[a]	20
C_{0h}, ng/mL	206.5 ± 145.4	360.3 ± 351.9
C_{min}, ng/mL	183.5 ± 150.6	294.3 ± 277.8
C_{max}, ng/mL	495.3 ± 453.2	756.6 ± 680.4
t_{max}, h	4.00 (2.00 - 8.00)	3.95 (2.00 - 6.07)
AUC_{12h}, ng.h/mL	4050 ± 3602	6141 ± 5586
$C_{ss,av}$, ng/mL	338.2 ± 299.4	513.0 ± 465.1
Fl Ind, %	96.82 ± 31.57	95.64 ± 26.41

[a] n=18 for AUC_{12h}, $C_{ss,av}$ and Fl Ind

A tendency for increased AUC_{12h} values was observed with increasing actual administered mg/kg doses (Figure 18).

Figure 18: Scatter Plot of AUC12h as a Function of the Actual Given Dose per kg for Stage 1 and Stage 2—Study TMC125-C126



For both stages, the exposure of TMC125 given as 4 mg/kg or as 5.2 mg/kg b.i.d. was higher in children ≥ 6 and < 12 years old compared to adolescents ≥ 12 and ≤ 17 years old (extremes included) (Figures 19 and 20, Table 17). This higher exposure in younger children was related to 1 outlier, no apparent cause could be established for this higher exposure and therefore the data was included. A large standard deviation (SD) was observed for the age group ≥ 6 and < 12 years old. Mean maximum plasma concentration was in both stages reached after 3 and 4 hours after intake of TMC125 for the youngest age group and the oldest age group, respectively.

Figure 19: Mean Plasma Concentration-Time Curves of TMC125 (Including SD Bars) After Administration of TMC125 4 mg/kg b.i.d. (Stage 1) for Both Age Groups

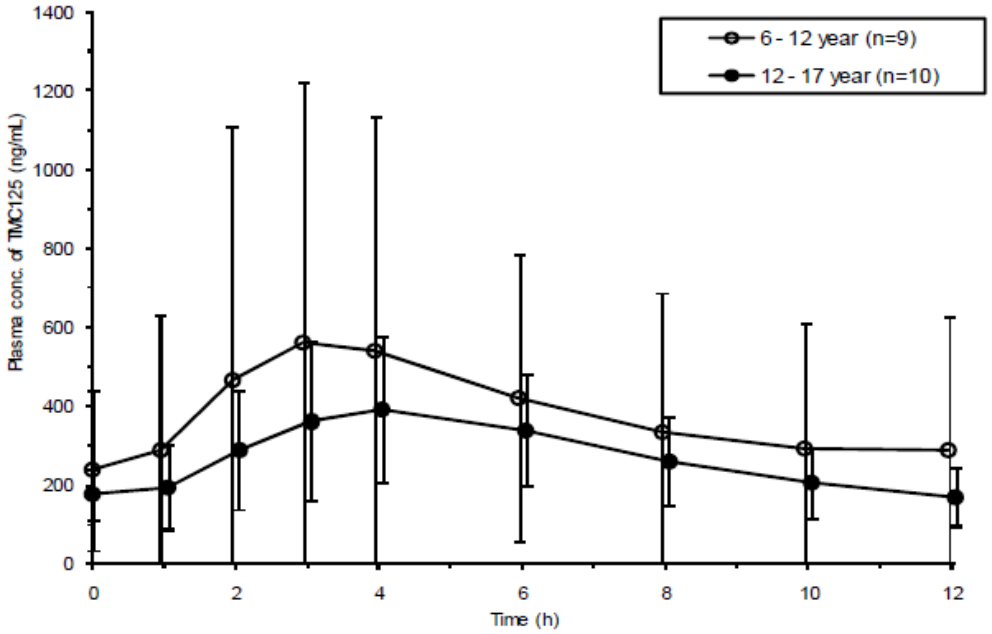


Figure 20: Mean Plasma Concentration-Time Curves of TMC125 (Including SD Bars) After Administration of TMC125 5.2 mg/kg b.i.d. (Stage 2) for Both Age Groups

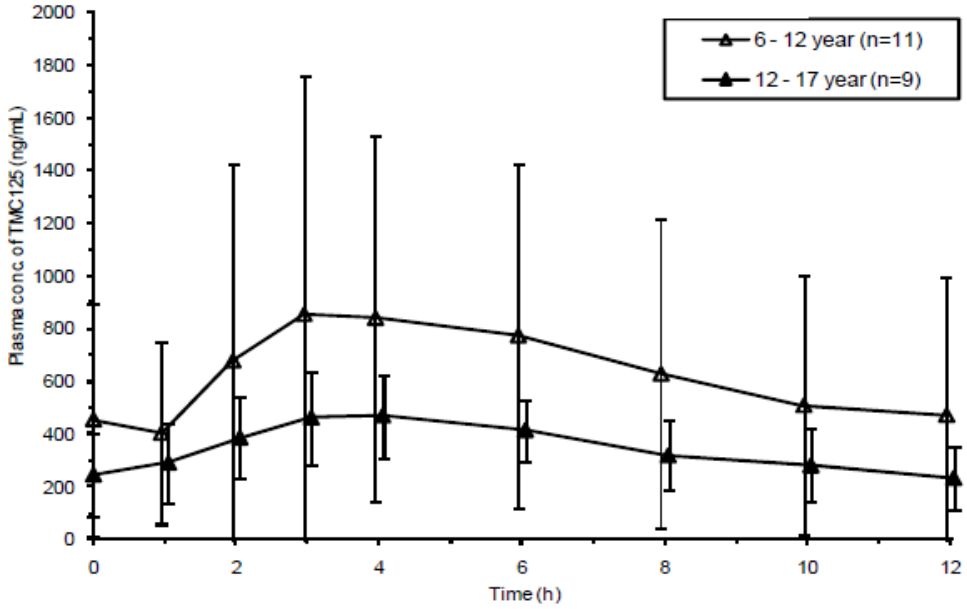


Table 17: Comparison of TMC125 Pharmacokinetics in Children and adults

Parameter	Mean (SD)							
	Adults		Children 6 to < 12 years		Adolescents 12 to < 18 years		All Children 6 to <18 years	
	200 mg b i.d. (DUET-1 and -2)	200 mg b.i.d. (TMC125-C228)	4.0 mg/kg b i.d.	5.2 mg/kg b i.d.	4.0 mg/kg b.i.d.	5.2 mg/kg b i.d.	4.0 mg/kg b.i.d.	5.2 mg/kg b.i.d.
N	575	27	9	11	10	9	19	20
AUC_{12h}, ng h/mL	5506 (4710)	3713 (2069)	4989 (5189)	7713 (7160)	3299 (1468)	4219 (1575)	4050 (3602)	6141 (5586)
C_{0h}, ng/mL	393 (391)	185 (128)	209 (210)	363 (352)	161 (70)	247 (155)	184 (151)	294 (278)
C_{max}, ng/mL	N/A	451 (232)	598 (635)	971 (866)	403 (181)	494 (144)	495 (453)	757 (680)

Originally, TMC125-C228 was chosen as the protocol specified reference for TMC125-C126 because it provided the pharmacokinetic parameters and associated variability of ETR administered as formulation F060 at a dose of 200 mg b.i.d. in treatment-experienced HIV-1 infected adults who were currently receiving a boosted protease inhibitor (PI) (primarily lopinavir co-formulated with low-dose ritonavir [LPV/rtv]). ETR dose of 4.0 mg/kg b.i.d. in children provided the comparable ETR exposure as compared to ETR dose of 200 mg b.i.d. in adults in Study TMC125-C228. However, the exposure to ETR in trial TMC125-C228 was low compared to the exposure recorded in other trials in which treatment-experienced HIV-1 infected adults were administered ETR as formulation F060 at a dose of 200 mg b.i.d., and during the conduct of Stage 2 of trial TMC125-C126 results from the Phase III trials TMC125-C206 and TMC125-C216 (hereafter referred to as the DUET-1 and -2 trials, respectively) became available demonstrating the efficacy, safety, and tolerability of ETR in adults over 24 and 48 weeks. It was therefore considered more appropriate to compare the exposures achieved in treatment-experienced HIV-1 infected pediatric subjects in trial TMC125-C126 with those in treatment-experienced HIV-1 infected adults participating in the DUET-1 and -2 trials.

This comparison indicated that when ETR was administered to pediatric subjects at the target weight-based dose of 5.2 mg/kg b.i.d. in trial TMC125-C126, the mean C0h and AUC12h of ETR were comparable to the values obtained in adults in the DUET-1 and -2 trials with the approved ETR dose of 200 mg b.i.d.

Safety: No SAEs were reported during this trial, in any stage. No consistent or clinically relevant changes over time in laboratory parameters were observed. Two subjects (1 subject in each stage) were reported with rash (i.e., grade 2 maculo-papular rash and grade 1 rash). These events were considered very likely and probably related to TMC125, respectively.

Conclusion: Based on the exposures of TMC125 achieved with TMC125 5.2 mg/kg b.i.d. and the overall safety and tolerability during Stage 2, the selected TMC125 dose of 5.2 mg/kg b.i.d. in children aged 6 to 17 for Phase II study is appropriate.

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/s/

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